Gastrointestinal symptoms and permeability in patients with juvenile idiopathic arthritis

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Abstract

Objective

Examining for gastrointestinal involvement in juvenile idiopathic arthritis is an important part of diagnostic and therapeutic procedures. Only few scientific data are available.

Methods

In a prospective study, 41 patients with juvenile idiopathic arthritis were examined for clinical and laboratory data of gastrointestinal involvement. Sugar absorption tests with lactulose, mannitol, and sucrose were applied to assess gastric and intestinal mucosal lesions. Faecal albumin and α1-antitrypsin levels were measured to examine gastrointestinal protein loss, a test for occult blood in stool was administered and Helicobacter pylori *serology was performed.*

Results

39% of our study population complained of chronic abdominal pain. The patient group showed increased sucrose excretion (p = 0.002), but a normal lactulose/mannitol ratio compared with healthy controls (p = 0.472). 21% of the patients had an elevated faecal α1-antitrypsin level, but only one patient showed occult blood loss. There was no correlation between risk factors and clinical or laboratory signs of gastrointestinal involvement.

Conclusion

We conclude that a high percentage of children and adolescents with juvenile idiopathic arthritis treated with non-steroidal antiinflammatory drugs show clinical or laboratory signs of gastrointestinal involvement.

Key words

Juvenile idiopathic arthritis, nonsteroidal anti-inflammatory drugs, intestinal and gastric permeability, gastrointestinal involvement, faecal α1-antitrypsin level.

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Introduction

Gastrointestinal symptoms like abdominal pain, dyspepsia or diarrhea are found in pediatric patients suffering from rheumatic diseases. These may be due to gastrointestinal involvement as has been shown in spondyloarthropathy (1), psychosomatic reactions (2), gastrointestinal toxicity of steroids and non-steroidal anti-inflammatory drugs (NSAIDs) (3). In addition, gastric and duodenal ulcers and gastrointestinal hemorrhage are observed without preceding clinical symptoms, perhaps as a consequence of the analgesic effect of NSAIDs.

In adults, endoscopy is a simple and tolerable diagnostic tool to rule out esophageal or gastric mucosal damage or colitis. However these procedures are invasive and cannot be used routinely as screening tests in the pediatric setting. Non-invasive screening tests designed to detect gastrointestinal lesions are needed.

This study was aimed at (1) collecting data about the frequency and intensity of gastrointestinal symptoms in pediatric patients with juvenile idiopathic arthritis, (2) assessing the relevance of predictive factors such as a family history of peptic ulcers and evidence of *Helicobacter pylori (H. pylori)* infection for gastrointestinal symptoms, and (3) evaluating the significance of NSAID – steroid combinations in gastrointestinal symptoms.

Materials and methods

Forty-one consecutive in-patient children and adolescents (25 female, 16 male; mean age 12.3 ± 2.8 years) with juvenile idiopathic arthritis (mean duration 4.4 ± 3.2 years) participated in this prospective study aimed at collecting data on gastrointestinal symptoms. The patients were recruited from the Department of Pediatric Rheumatology at the North-west German Center for Rheumatology. The patients were retrospectively identified according to the International League Against Rheumatism (ILAR) criteria (4). Patients with systemic juvenile idiopathic arthritis were included according to the ILAR criteria, as the disease has no increased risk of gastrointestinal vasculitis. Amyloidosis was excluded in this group of patients. Also patients with connective tissue diseases and vasculitis were excluded because of the risk of gastrointestinal vasculitis caused by the disease process itself.

The examination of each patient comprised:

1. A standardized questionnaire on abdominal pain (including questions about the frequency, intensity and duration of abdominal pain, awaking due to abdominal pain,and social consequences of abdominal pain like consulting a doctor, taking drugs and missing school because of pain within the last six months). The possible answers were summarized on an "abdominal pain index" (maximal value 14).
2. A standardized questionnaire on further gastrointestinal symptoms such as dyspepsia, vomiting, loss of appetite, meteorism, regurgitation and retrosternal pain. The possible answers were summarized using a "gastrointestinal symptom index" (maximal value 10). Additionally, two questions were asked about frequency and consistency of stool – the answers were summarized in a "stool index" (maximal value 6).
3. A standardized questionnaire on body complaints with a scale for gastric problems (5).
4. A questionnaire regarding chronic abdominal pain, gastritis and peptic ulcer in first- and second-degree relatives.
5. A questionnaire on active and passive nicotine abuse.
6. Collection of data on the duration of the disease and on medication.
7. Checking the stool for occult blood (Hexagon Obti Test, monoclonal anti-human Hb: kit Human, Taunusstein, Germany) (6).
8. Examination of protein loss using the faecal α1-antitrypsin level (normal values < 2.5 mg/g of wet stool; commercial kit by Bioscientia, Mainz, Germany) and by testing albumin in the stool with a qualitative test (BM-Test, Boehringer, Mannheim, Germany (7)).
9. Testing for IgG-, IgM- and IgA-antibodies against *Helicobacter pylori* (ELISA), positive result ≥ 10 U/l)

10. Investigation of gastric permeability by measuring sucrose permeability (8) and of intestinal permeability by determining lactulose/mannitol permeability (9).

Permeability testing was performed in 33 patients. Following an overnight fast, a pre-test urine sample was collected. Then patients received a solution (5 g lactulose, 1 g mannitol and 75 g sucrose in 200 ml of water; osmolarity 1200 mosmol/l) per os. Urine was collected after a further fasting period of 5 hours. During this time a small volume of water was permitted. Urine was stored in a container with 0.1 ml thimerosal 1% for preservation. 20 ml of the collected urine was stored at -20° C. Measurement of urinary sugars was performed by capillary gas chromotography and mass spectrometry.

Sample preparation
After determination of creatinine, the pH of the urine was measured and adjusted to pH 5-7 with 1 mol/l HCl and centrifuged at 4000 x g for 10 minutes at room temperature. The volume corresponding to a content of 1 mmol of creatinine was taken and evaporated to dryness at 60°C under constant flow of nitrogen. The dry residues of urine were derived by adding 300 µl Tri-sil-TBT and heated for 30 minutes at 100°C. After cooling, the derivatives were diluted with 1 ml distilled water and extracted with 1 ml hexane. The hexane layers were collected after centrifugation at 4000 x g for 10 minutes at -19°C. 25 µl bistrimethylsilyltrifluoroacetamide was added.

Gas chromatography
2 µl portions were automatically injected into a gas chromatograph (Model 5890, Hewlett Packard Co., Amstelveen, Netherlands). The column was a 30 m x 0.32 mm capillary fused silica with a film thickness of 0.25 µm. The gas flow rate was 0.6 ml/min, split ratio 1:15, detector temperature 300°C, and injector temperature 280°C. Oven program: start at 120°C, increase by 3°C/min to 240°C, then increase by 10°C increments to a final temperature of 365°C (10).

Identification and quantification
Identification and quantification of the urinary mannitol, lactulose, and sucrose were performed by mass spectrometry (Model 5972, Hewlett Packard Co.,Amstelveen,Netherlands). The results were given as the area under the curve ratio of lactulose/mannitol for intestinal permeability and as the area under curve of sucrose for gastric permeability.

Control group
For study immanent validity, we selected two control groups. The first, the pathological control group, comprised 7 patients with active chronic inflammatory bowel disease (IBD) and a mean age of 15.7 ± 2.2 years. For the second, the normal control group, we enrolled 11 volunteers with no history of gastrointestinal or rheumatic symptoms or of current drug intake (mean age 19.3 ± 4.6 years). Age-related differences in gastrointestinal permeability are unlikely in the second decade (11, 12).
Statistical analysis was based on the Mann-Whitney-U-test and Student's t test for unpaired samples where appropriate. The analyses were done with SPSS, version 11.0 for Windows. The study protocol was approved by the Medical Ethics Committee of the University of Münster (Germany).

Results

Of the 41 patients taking part in the study, 4 had the systemic form of juvenile idiopathic arthritis, 10 persistent oligoarthritis, 5 extended oligoarthritis, 12 polyarthritis (rheumatoid factor negative), and 10 an enthesitis related arthritis.

Prevalence of abdominal symptoms
16 patients (39%) had chronic abdominal pain at least once a month, 11 (27%) at least once a week. In 8 patients, the pain was so strong that the children had to stop their daily activities. Twelve (29%) missed school due to abdominal pain, 9 consulted a doctor, and 8 usual took drugs to relieve the pain. In the standardized questionnaire surveying physical complaints (5), 9 patients had values > 1.5 SD above the mean on the scale of abdominal pain.
Dyspepsia, vomiting, loss of appetite, meteorism, regurgitation or retrosternal pain summarized in the gastrointestinal symptom index were reported infrequently as a chronic problem. Related to a maximum possible index value of 10, the mean index in our study group was 3 (range 0 – 8). No patient reported an abnormal stool consistency.

Laboratory tests
Only one patient presented with occult gastrointestinal blood loss as revealed by the Hexagon Obti test. In this patient, gastroduodenal endoscopy showed a gastric ulcer. None of the patients had a positive result for intestinal loss of albumin, nine had a pathological faecal α1-antitrypsin level. 11 of 34 patients had at least one positive Helicobacter antibody titer.

Gastric and intestinal permeability
33 children were examined for gastric and intestinal permeability. The L/M ratio and the area under the curve of sucrose in urine are shown in Table I.
As expected, the healthy controls showed the lowest excretion of sucrose and lactulose/mannitol ratio in urine, and patients with active inflammatory bowel disease the highest values. The Mann-Whitney U-test revealed that the IBD patients excreted significantly more sucrose ($p = 0.026$) and lactulose/mannitol ($p = 0.004$) than healthy subjects. Additionally, the L/M ratio was significantly increased compared to patients with juvenile idiopathic arthritis ($p = 0.002$). Only one patient with juvenile polyarthritis (rheumatoid factor negative) showed an L/M ratio (0.132) above the mean (0.067) of the L/M ratio in the group of IBD patients. Sucrose values did not differ between these two groups ($p = 0.463$). Patients with juvenile idiopathic arthritis excreted significantly more sucrose than healthy controls ($p = 0.002$), but the L/M ratio was not significantly different ($p = 0.472$). In comparison of gastric and intestinal permeability between the main diagnostic subgroups of our cohort (persistent oligoarthritis, polyarthritis RF negative and enthesitis

related arthritis) no significant difference were found in L/M ration, but patients with polyarthritis (RF negative) excreted more sucrose (median: 895; 207 to 2111) than patients with enthesitis related arthritis (median; 437; 80 to 875) (p = 0.018). Although in the whole study group no significant correlation between clinical parameter (abdominal pain index) and sucrose excretion could be found (Spearman correlation coefficient 0.293; p = 0.097), the patients with polyarthritis showed in tendency a higher abdominal pain index than patients with enthesitis related arthritis (p = 0.075).

Intestinal permeability was not correlated with any anamnestic or clinical parameter. The patients with elevated faecal α1-antitrypsin levels had not a higher sucrose excretion (p = 1.0) or L/M ratio (p = 0.54) than the patients without signs of gastrointestinal protein loss. Sucrose excretion was not significant different in the group with a positive H. pylori serology (1029 ±1108) in comparison to the group with negative H. pylori serology (793 ± 1013) (p = 0.667). Furthermore these two groups did not differ significantly in their L/M ratios (0.01 ± 0.009 vs. 0.013 ± 0.028).

Finally, no significant correlation was found between sucrose excretion (r = - 0.11) or the L/M ratio (r = - 0.26) and the duration of the idiopathic arthritis.

Antirheumatic drugs

Of the 33 patients tested for intestinal permeability, 19 took NSAIDs (15 naproxen,3 indomethacin, 1 ibuprofen) without steroids, 14 were treated with NSAIDs (4 naproxen, 9 indomethacin, 1 ibuprofen) in combination with steroids. Additionally, the majority of patients in both groups (11/19 versus 13/14) took further slow-acting antirheumatic drugs such as methotrexate or azathioprine.

In the Mann-Whitney U- test, the L/M ratio (p = 0.759) and sucrose excretion (p = 0.161) did not differ between patients taking NSAID therapy with or without steroids. Furthermore, no difference was found between patients who were treated with methotrexate in contrast to patients without methotrexate (L/M ratio p = 0.573; sucrose excretion p = 0.181).

Table I. Mean sucrose values and L/M ratio (± SD) in the index group with juvenile idiopathic arthritis, in healthy controls and in the controls with IBD.

		Area under curve values of sucrose (mean ± SD)	L/M ratio (mean ± SD)
Healthy controls	(n = 11)	275 (±191)	0.007 (± 0.006)
Index group	(n = 33)	899 (± 813)	0.012 (± 0.023)
Controls with IBD	(n = 7)	3300 (± 3693)	0.067 (± 0.075)

Discussion

This study examined clinical observations and laboratory tests for gastrointestinal symptoms and involvement in children with juvenile idiopathic arthritis. In adults, gastrointestinal inflammation has been documented as part of specific rheumatic diseases (1) and as NSAID enteropathy (3). Up to 48% of patients with spondyloarthropathy, but only up to 15% of patients with rheumatoid arthritis, had a prevalence of histological signs of inflammation (13). This difference is discussed as a factor playing an important role in the etiopathogenesis of enteropathy, making a primary genetic defect likely (14). The prevalence of gastrointestinal complications of NSAIDs ranges from 10 to 20% for dyspepsia and from 1 to 2% for serious side effects (3). The mechanism of gastrointestinal irritation and bleeding involves both inhibition of prostaglandin synthesis and direct chemical damage to the gastric and intestinal mucosa. However data on the prevalence of clinical and laboratory signs of gastrointestinal involvement in juvenile idiopathic arthritis are sparse.

Chronic recurrent abdominal pain affecting normal activity has been reported in 10 to 15% of school-age children (15). In our study group, 39% of the children reported chronic abdominal pain during the last 6 months. This is a higher percentage than reported in a former study of children with rheumatic diseases (16), but compatible with the results by Len *et al.* (17). However, in our study only one patient presented with gastrointestinal bleeding as a sign of gastric ulcer, and this was the only patient enrolled in our study in whom NSAID therapy had to be discontinued. In contrast, in a retrospective study by Barron *et al*. (18), 10% of the patients stopped their NSAID intake due to abdominal pain. The lowest prevalence of abdominal pain reported in the study by Dowd *et al.* (16) could have resulted from the retrospective study design. In our experience, most children reported symptoms only if they were explicitly asked. Firstly, we have to consider the social aspects of abdominal pain in this patient group. 29% of our patients missed time at school, and 22% consulted a physician due to abdominal pain. Other gastrointestinal symptoms were reported infrequently; as in other studies these were seldom a reason to stop NSAID medication (18).

Nine patients had a high level of faecal α1-antitrypsin as a sign of possible intestinal protein loss. This parameter is not correlated with abdominal pain. The relevance of abdominal pain as an indicator of intestinal or gastric NSAID induced injuries is controversially discussed (16, 19, 20). Faecal α1-antitrypsin has been suggested as a reliable marker for intestinal mucosal lesions (21), but not for gastric ulcer or gastritis, although other feacal proteins like calprotectin have recently been used to detect NSAID enteropathy (22). Our data concerning the discrepancy between α1-antitrypsin levels and intestinal permeability are in conflict with the study by Picco *et al*. (23). This may be due to the high percentage of patients with spondyloarthropathy in the study by Picco *et al.* Subjects in this diagnostic group have primarily a higher risk of intestinal inflammation (13) and impaired intestinal permeability (14). Our study group consisted mainly of patients with juvenile oligo- or polyarthritis who showed no difference in L/M ratio compared with controls.

Additionally, it is possible that intestinal permeability and protein loss may be parameters for different intestinal lesions in children with juvenile idiopathic arthritis. In the literature a discordance of gastrointestinal protein loss measured by fecal α1-antitrypsin levels and altered intestinal permeability measured by the L/M ratio is reported in context of several diseases. Alam *et al*. (24) reported an improvement of intestinal permeability in children with acute shigellosis treated with zinc supplementation, but enteric α1-antitrypsin clearance was not influenced, although in another study a strong correlation between intestinal permeability and fecal α1-antitrypsin level in children with a gastrointestinal infection disease was reported (25). No clear relationship between gastrointestinal permeability to oligosaccharides and fecal α1-antitrypsin was found in children with atopic dermatitis (26). Perhaps these different findings with respect to the accordance of L/M ratio and fecal α1-antitrypsin loss are caused by different levels of gastrointestinal lesions. In practice both procedures are independent supplementary variable for the detection or monitoring of intestinal lesions.

It has been shown that increased permeability for sucrose is a good marker for gastric mucosal damage in adults (8) as well as in children (27). The significantly increased sucrose excretion in our study group compared with healthy controls is compatible with NSAID effects (28, 29). However, in another study no correlation was shown between endoscopically documented mucosal lesions and sucrose permeability (30). We found no correlation between sucrose permeability and various risk factors for gastric lesions such as nicotine consumption, a positive family history of gastric ulcer and gastritis, or positive *H. pylori* serology. In our study, a positive *H. pylori* serology was seen as evidence of contact between the person and bacteria in the past, not as a parameter for a current infection or for an *H. pylori*-induced gastric mucosal lesion. In our population of children and adolescents with juvenile idiopathic arthritis and NSAID therapy, we found no increase in sucrose permeability if the patients additionally had a positive *H. pylori* serology. A synergistic relation between the presence of *H. pylori* and NSAID use is being debated (31, 32). In children, eradication of *H. pylori* had no significant effect on the healing of gastric ulcers associated with longterm NSAID use (33).

Although an *H. pylori*-specific serum IgG response is highly specific (99%) and sensitive (96%) in children (34), the accuracy of serology for the detection of *H. pylori* colonization of the gastric mucosa is limited (35). Interestingly, patients taking NSAIDs in combination with steroids did not differ in their sucrose permeability. In adults, steroids are discussed as a risk factor for NSAID-induced gastric ulcers only in an odds ratio of 2.2 (36) to 2.5 (37). However, in former studies with children (16), the exclusion of prednisone users from those taking NSAIDs did not affect the incidence of lesions.

Several studies have shown that the risk of NSAID-induced gastrointestinal complications is increased mainly during the first 3 months of treatment (38). This factor may be the reason for the lack of correlation between the duration of NSAID therapy and the permeability parameters in our study. Most of our patients had taken NSAIDs for more than half a year. Also the patients who were treated with MTX had no higher sucrose excretion or L/M ratio. Our cohort is too small for further statistical analysis, which calculated the effect of different drug combinations or combination of diagnosis and specific drugs.

In conclusion, this study provides evidence that a significant number of children with juvenile idiopathic arthritis show clinical and laboratory signs of gastrointestinal involvement. These are due to chronic inflammation through the underlying disease and drug effects of NSAIDs. The importance of these factors in detecting gastric or intestinal mucosal lesions is unclear, especially as no significant correlation was found between these non-invasive parameters. Further prospective studies with endoscopic evaluation of non-invasive results need to be carried out in children to investigate the clinical implications of these results. Until those results are available careful examination of gastrointestinal symptoms is mandatory in children suffering from juvenile idiopathic arthritis and taking NSAIDs.

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